(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/17820 A1

(51) International Patent Classification[7]: A61F 2/30, 2/28, A61L 27/30

(21) International Application Number: PCT/NL01/00589

(22) International Filing Date: 2 August 2001 (02.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1016040 29 August 2000 (29.08.2000) NL

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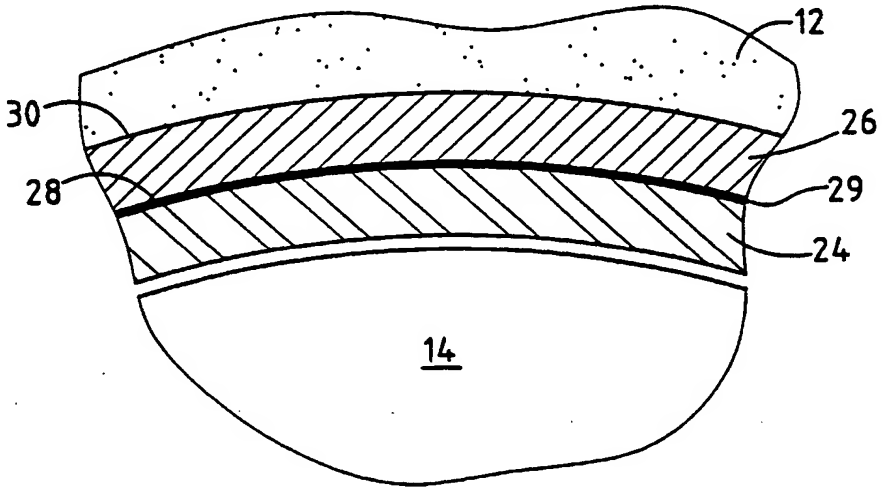
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: POROUS ATTACHMENT MATERIAL FOR CELLS



(57) Abstract: A porous attachment material (18; 20; 26) for cells, in particular bone (cells), comprises a foam which is metallized with a biocompatible metal or metal alloy. The attachment material has interconnected pores. According to the invention, the foam is a non-carbonized polyurethane foam or polyether foam. A gradual transition in the porosity increases the possible applications. Attachment material can also be used for the in-vitro culturing of cells.

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Porous attachment material for cells

According to a first aspect, the present invention relates to a porous attachment material for cells, in particular bone (cells), comprising a foam which is metallized with a biocompatible metal or metal alloy, the attachment material having interconnected pores.

An attachment material of this type is known, for example from United States Patent US-A-5,282,861. This known attachment material is used as a replacement material for spongy (cancellous) bone and/or to receive cells and tissue, since it has a structure which resembles spongy bone of this type, which promotes bone (in)growth. This attachment material is produced by using a chemical vapour deposition method to deposit a biocompatible metal or metal alloy, in particular tantalum or alloys thereof, on a substrate with a foam structure which is produced, for example, from carbon, graphite or ceramic material. Tantalum is used because it has long been known to have favourable properties for use as an implant material both for bone and tissue. This known attachment material is lightweight, strong, has a porous structure resembling the microstructure which is present in natural spongy bone and acts as a matrix for receiving bone, as well as providing permeability and a high specific surface area to promote the ingrowth of new bone.

One drawback of this known attachment material is its costs on account of the chemical vapour deposition (CVD) technique which is used, and the associated time required. Furthermore, CVD is a rather complex process. To deposit the biocompatible metal or metal alloy in the desired thickness, a long process time is required. In addition, for economic feasibility, it is important for the network structure of the carbon-containing foam to be reproducible. However, US-A-5,282,861 lacks any details about the production or origin of the foam. This reproducibility leaves something to be desired with many materials, however. Furthermore, this known attachment material is rigid, whereas for many applications a flexible attachment material is preferred with a view to the required shaping. This rigidity is inherent to the step of carbonizing plastic foam which is used in the production of the carbon-containing foam. This carbonization step is required in order to make the foam sufficiently heat-resistant to be able to withstand the temperature of 1100°C which prevails during the

CVD of tantalum; otherwise, the original foam would be destroyed at this temperature.

When an implant is to be made, first the attachment material of this kind is to be produced, whereafter an insert, e.g. from PE, is bonded thereto by compression moulding. The required shape is applied to the implant by further machining operations of the product prior or after compression moulding. This further machining causes struts having an open end to be present, which can raise toxicity problems due to exposure of the bone to carbon. The X-ray permeability of tantalum is relatively weak, which causes diagnostic examination after surgery to be difficult.

It is an object of the present invention to at least partially eliminate the abovementioned drawbacks.

For this purpose, in the porous attachment material of the type according to the invention described in the introductory part, the foam is a non-carbonized polyurethane foam or polyether foam. These types of foam have a network structure of interconnected pores which can be produced reproducibly. In addition, the use of these types of foam for the production of the porous attachment material according to the invention allows metallization techniques which are quicker than CVD to be used. Consequently, the total production costs of the attachment material according to the invention are lower than those of the attachment material according to the above prior art. Furthermore, depending on the metallization technique selected, the network structure of polyurethane foam and that of polyether foam allows the quantity of metal which is deposited to be controlled accurately, so that the porous attachment material according to the invention can also be produced in relatively flexible embodiments. This flexibility allows easy deformation of the attachment material according to the invention. Moreover, the pore structure of polyurethane foam and that of polyether foam resemble the network structure of the pores in spongy bone, which promotes the growth of cells. It is also possible to control the pore structure of the foam.

Polyurethane is preferred to polyether foam with a view to reproducibility.

The dimensions of the interconnected pores of the attachment material preferably lie in the range from 50-1000 micrometers. The porosity is preferably in the range from 50-96%. These values for the pore dimensions and the porosity of the attachment material according to the invention correspond to the values of the pores in natural

bone, so that the attachment material starts to be biologically and mechanically incorporated when used in the body. The lower limit of 50 micrometers for the pore dimensions is determined by the conditions which are required for the formation of new blood vessels, known as angiogenesis.

According to a particularly preferred embodiment, the attachment material has a gradual change in porosity from low porosity, such as 50% or more, for example 70%, to high porosity, such as 96%, as seen in the thickness direction of the attachment material. A gradual change in porosity of this nature leads to a gradual transition between the natural bone and the implant in which the attachment material is used, the side of the attachment material with the highest porosity facing towards the bone and the side with the lowest porosity, which has a relatively dense attachment surface, adjoining, by way of example, a solid section of a prosthesis. Within certain limits, the side with the high porosity can be deformed better and therefore adapted to the adjoining bone. At the moment of use during implantation, therefore, there is a large contact area between bone and attachment material and optimum conditions for bone (in)growth are created.

According to a further variant of this embodiment, the attachment material comprises a dense, non-porous surface layer of the biocompatible metal or metal alloy adjoining the side of low porosity. In other words, there is a solid surface layer of biocompatible material on one side of the attachment material, offering a good attachment surface for a solid part of a prosthesis, for example a prosthesis socket which is made from plastic.

The biocompatible metal or metal alloy is preferably selected from the group consisting of Ti, TiNb, TiV, Ta, TaNb, CoCr, CoCrMo and stainless steel, alloys and combinations thereof. Titanium and titanium alloys, such as for example Ti6Al4V are preferred, on account of their proven biocompatibility, as well as their commercial acceptance.

The thickness of the porous attachment material is dependent on its use. By way of example, the thickness of the attachment material is of the order of magnitude of up to 20 mm for cages used in the spinal column, while for other positions and functions the thickness is usually of the order of magnitude of 0.3-4 mm. For particular applications, for example in oncology, it may be thicker.

The attachment material according to the invention may be

provided in its pores with an additional upper layer of a calcium-containing and/or phosphate-containing material. Examples of such materials include hydroxyapatite (HA), fluoroapatite, tricalcium phosphate (TCP) and tetracalcium phosphate, octocalcium phosphate (OCP), brushite (a precursor of HA), calcium carbonate, and the like, which further improve the biocompatibility properties of the attachment material according to the invention. Agents which stimulate bone growth, angiogenesis-stimulating agents, antibacterial agents and/or anti-inflammatories may also be provided in the pores in order to accelerate the growth process of the cells and to prevent infections.

A second aspect of the invention provides a method for producing a porous attachment material for cells, in particular bone (cells), in which a biocompatible metal or metal alloy is applied to the pore walls of a foam, the foam having interconnected pores, which method according to the invention is characterized in that a plastic foam which is selected from a non-carbonized polyurethane foam or polyether foam is used.

The attachment material may be produced using a multistage process, in which case in a first step a thin, first starting layer of metal or metal alloy is deposited by means of a physical vapour deposition (PVD) process, and in a second step a thicker layer of the biocompatible metal or metal alloy is deposited by means of an accelerated deposition process, in particular physical vapour deposition processes, such as HS-PVD (high-speed PVD) or LPPS (low-pressure plasma spraying) or EB-PVD. The layer thickness of the thin, first starting layer which is deposited using conventional PVD is preferably of the order of magnitude of a few µm to a few tens of µm, usually of the order of magnitude of at least 5 µm. Conventional PVD is used to deposit the starting layer, since the quicker methods cannot be used without the risk of damaging or destroying the foam structure of the plastic substrate on account of the high temperatures prevailing. Once a starting layer of sufficient thickness (for example 5 µm) and strength has been deposited, the deposition can be continued, depending on the application varying, for example, from 30 to 1000 µm, with the aid of quicker methods, since the starting layer protects the underlying foam structure of the substrate to a sufficient degree. HS-PVD is preferred, since this technique allows the thickness of the amount of metal deposited on the starting layer which has been formed to be controlled reliably

and therefore, if desired, allows a gradual transition in the porosity from high to relatively low to be achieved. The quality and composition of the target used also plays a role in the gradual transition. Other production techniques or combinations, such as electroplating, electroless plating, sputtering, plasma spraying (at low pressure) and sintering are also among the possible options.

With a view to the overall production time, the method according to the invention is preferably carried out as a single-step process, in which the full layer thickness is applied in one operation and in which the settings of a HS-PVD device used for this purpose are adjusted during the process in such a way that a lower energy level is used at the start, in order not to adversely affect the structure of the polyurethane foam, while after a sufficient thickness and strength has been reached the energy level is increased. However, it is not then necessary to interrupt the vacuum. In this preferred embodiment the initial metal deposit is applied at a low temperature, while after a certain thickness of the metal deposit has been achieved the temperature may be raised and accordingly the deposition rate can be increased. In such an embodiment the initial metal deposit protects the foam structure against deterioration.

In order to improve the surface characteristics of the attachment material according to the invention the manufacturing method advantageously comprises a finishing step, wherein a thin layer of a metal or metal alloy, preferably titanium of its alloys, is applied by electroplating. For example, an ectroplated finishing layer has an improved smoothness compared to a surface layer deposited by PVD.

In an alternative embodiment in a first step a thin, first starting layer of metal or metal alloy is deposited by means of a physical vapour deposition process, and in a second step a thicker layer of metal or metal alloy, preferably titanium or its alloys, is electroplated. In this embodiment growth of the initial skeleton and application of a finishing layer is combined. A pyrolysis step may be carried out before or after the second step.

Here it should be noted that in production methods wherein a coating solution containing metal particles is applied at low temperature, a coherent metal structure is obtained by sintering at high temperature. However the increase of the temperature will cause the plastic foam structure to be destroyed before the coherent metal

structure has been produced. This is a serious drawback with respect to the final quality of the attachment material thus obtained. In addition, the repeatibility and reproducebility will be low.

According to a further aspect, the invention provides an implant which is characterized in that at least a section thereof comprises a porous attachment material according to the invention, as described above. Examples of implants include, inter alia, a total hip prosthesis, comprising both the femur and acetabulum components, a total knee prosthesis, comprising both the femur and tibia components, a shoulder prosthesis, a finger prosthesis, cages (intervertebral spacers), dental/dental surgery implants, soft parts of anchors, and implants for oncology. The attachment material according to the invention may be attached to a solid metal part, for example in the shape of a shell, in which a polyethylene insert is immovably positioned, for example by means of diffusion welding or electroplating. Unlike in the prior art, in which the insert is fixedly joined to the attachment material by means of compression moulding, in an implant according to the invention the insert may be exchangeable. The desired strength of the attachment material according to the invention is partly determined by its use. By way of example, the tensile and compressive strengths of trabecular bone are on average 10 MPa. Since bone has the potential of self-regeneration after traumatic damage, the structure of the porous attachment material according to the invention, which does not inherently have a self-regenerating capacity, will have to be stronger than the adjoining bone. Taking into account a safety margin, the adhesion material according to the invention for load-bearing applications preferably has a tensile strength of more than 20 MPa, a compressive strength of more than 20 MPa, a shearing stress of more than 7 MPa and a Young's modulus of elasticity of 1 GPa.

A further aspect of the invention relates to a method for the in-vitro culturing of cells, in particular bone cells, on a substrate in a culture medium, in which a substrate comprising biocompatible material has a foam structure of interconnected pores, and wherein a load is applied periodically or continuously to the substrate. In this aspect of the invention, the substrate may be produced from any biocompatible material, provided that it has a structure of interconnected pores. Preferably, the substrate used is a porous attachment material according to the invention, as described above. In this method, cells, for example bone marrow or cartilage cells,

are cultured in a suitable liquid culture medium which contains the required growth substances, on the substrate. During culturing a load is applied, which is beneficial or even a requirement for the successful growth of cells, in particular bone cells and cartilage cells. For example, the substrate may be contacted with a reciprocating brush or roller which exerts a stress on the substrate. After sufficient cell material has been cultured, the cell material obtained can be processed further in various ways. By way of example, the cell material formed can be removed from the substrate and be introduced immediately into the patient. In this variant, the reproducibility of the network structure of the pores is less important. The cell material formed may also be implanted together with the substrate, in which case the preferred embodiments of the attachment material according to the invention which have been discussed above are advantageously employed for the substrate.

According to yet another aspect, the invention provides a porous attachment material for cells, in particular bone (cells), which attachment material comprises a foam of interconnected pores of a biocompatible material, which is characterized in that the attachment material has a gradual change from low porosity, for example of 50% or more, such as 70%, to a high porosity, such as 96%, as seen in the thickness direction. As stated above, this gradual change offers a gradual transition between bone and implant, of which the attachment material forms part. Better deformation properties and a larger contact area are other advantages. Preferably, the section of low porosity of 50% is provided with a dense, non-porous surface layer of the biocompatible material. The other preferred embodiments described above are also advantageously applied to this aspect of the invention.

The invention will be explained below with reference to the appended drawing, in which:

Fig. 1 diagrammatically depicts an example of a prosthesis in cross section, in which an attachment material according to the invention is present at various locations; and

Fig. 2 shows a detail from Fig. 1.

Fig. 1 shows a diagrammatic cross section through a prosthesis, for example a hip or knee prosthesis, which is denoted overall by reference numeral 10, while natural bone is denoted by reference numeral 12. A head 14 of the prosthesis 10 is solid and consists of a biocompatible metal or ceramic, for example CoCrMo, Al_2O_3 or yttrium-

stabilized zirconia. A support part 16 for the head 14 is provided with a layer of attachment material 18 according to the invention. Furthermore, the support part 16 comprises an insert 20 of attachment material according to the invention, which functions as bone substitute, for example when removing a damaged joint surface. A socket 22 of the prosthesis has a layered structure and comprises, from the inside outwards, a polyethylene layer 24, which is in contact with the solid head 14, and a layer 26 of attachment material according to the invention. The layered structure is illustrated in more detail in Fig. 2, using the same reference numerals for the same components. As can be seen from that figure, the surface 28 of the attachment layer 26 is provided with a dense surface layer 29 (illustrated in black) and therefore provides a good attachment surface for the polyethylene or ceramic insert 24. The attachment layer 26 has a network structure of interconnected pores, in which the porosity is graduated, from 65% in the vicinity of the surface 28 to 95% on the surface 30 which comes into contact with the bone 12.

In examples described below for the production of an attachment material according to the invention, the starting material used was a commercially available PU foam with an average of 63 pores per inch and with pore dimensions in the range from 400-500 micrometers. The thickness of the PU foam was on average 2 mm.

The PU foam was provided in one step with a titanium layer with a layer thickness of 50 micrometers, using conventional PVD. Then, the plastic foam matrix was removed by pyrolysis. By means of a heat treatment under reducing conditions, the titanium foam obtained was brought to its primary ductility. The foam obtained in this way was a flexible attachment material for bone cells which was also eminently suitable as a substrate for the in-vitro culturing of cells.

Another piece of the same PU foam was provided, by means of conventional PVD, with a thin layer of titanium with a thickness of 5 micrometers, after which a heat treatment was used to remove the PU matrix by means of pyrolysis, and the titanium foam obtained was brought to its primary ductility by means of a heat treatment. By means of a physical vapour deposition method using HS-PVD, the layer thickness was increased to 50 µm. The titanium foam thus produced had a porosity, which changed gradually from 65% to 95% on the side closest to the target.

Depending on the conditions, the separate pyrolysis step may be omitted. In such an embodiment during the second PVD step the

temperature of the substrate is raised in such a way that pyrolysis occurs automatically.

A finishing layer of titanium can be applied by electroplating in order to improve the surface properties of the foam thus produced.

C L A I M S

1. Porous attachment material (18; 20; 26) for cells, in particular bone (cells), comprising a foam which is metallized with a biocompatible metal or metal alloy, the attachment material having interconnected pores, characterized in that the foam is non-carbonized polyurethane foam or polyether foam.

2. Attachment material according to claim 1, characterized in that the dimensions of the interconnected pores lie in the range from 50-1000 µm.

3. Attachment material according to claim 1 or 2, characterized in that the porosity lies in the range from 50-96%.

4. Attachment material according to one of the preceding claims, characterized in that the attachment material exhibits a gradual change in the porosity, as seen in the thickness direction.

5. Attachment material according to one of the preceding claims, characterized in that a section (28) of low porosity is provided with a dense, non-porous surface layer (29) of the biocompatible metal or metal alloy.

6. Attachment material according to one of the preceding claims, characterized by a porosity which resembles that of a porous bone.

7. Attachment material according to one of the preceding claims, characterized in that the biocompatible metal or metal alloy is selected from the group consisting of Ti, TiNb, TiV, Ta, TaNb, CoCr, CoCrMo and stainless steel, alloys and combinations thereof.

8. Attachment material according to claim 7, characterized in that the biocompatible metal or alloy comprises titanium or a titanium alloy.

9. Attachment material according to one of the preceding claims, characterized by an additional upper layer of a calcium-containing and/or phosphate-containing material in the pores.

10. Attachment material according to one of the preceding claims, characterized in that the attachment material is provided in the pores with one or more agents which stimulate bone growth, angiogenesis-stimulating factors, anti-bacterial agents and/or anti-inflammatories.

11. Method for producing a porous attachment material for cells, in particular bone (cells), in which a biocompatible metal or metal alloy is applied to the pore walls of a foam, the foam having interconnected pores, characterized in that a plastic foam which is selected from non-carbonized polyurethane foam or polyether foam is used.

12. Method according to claim 11, characterized in that in a first step a thin, first starting layer of metal or metal alloy is deposited by means of a physical vapour deposition process, and in a second step a thicker layer of the metal or metal alloy is deposited by means of an accelerated deposition process.

13. Method according to claim 11, characterized in that the entire layer thickness is applied in one operation using an accelerated PVD process, work being carried out at a low energy level during a first part of the process, during which a thin, first starting layer of metal or metal alloy is deposited, and then a thicker layer being deposited in a second part at a high energy level.

14. Method according to anyone of claims 11-13, characterized in that the method also comprises a finishing step, wherein a thin layer of metal or metal alloy, preferably titanium or its alloys, is applied by electroplating.

15. Method according to claim 11, characterized in that in a first step a thin, first starting layer of metal or metal alloy is deposited by means of a physical vapour deposition process, and in a second step a thicker layer of a metal or metal alloy, preferably titanium or its alloys, is electroplated.

16. Method according to anyone of claims 12-15, characterized in that the layer thickness of the thin, first starting layer is at least 5 µm.

17. Implant, characterized in that at least a section thereof comprises a porous attachment material according to one of the preceding claims 1-10.

18. Method for culturing cells, in particular bone cells, in vitro, on a substrate in a culture medium, wherein a foam structure of interconnected pores of a biocompatible material is used as the substrate, to which a load is applied.

19. Method according to claim 18, characterized in that a porous attachment material according to one of the preceding claims 1-10 is used as the substrate.

20. Porous attachment material for cells, in particular bone (cells), comprising a foam of interconnected pores of a biocompatible material, characterized in that the attachment material has a gradual change in porosity, as seen in the thickness direction.

21. Porous attachment material according to claim 20, characterized in that a section (28) of low porosity is provided with a dense, non-porous surface layer (29) of the biocompatible material.

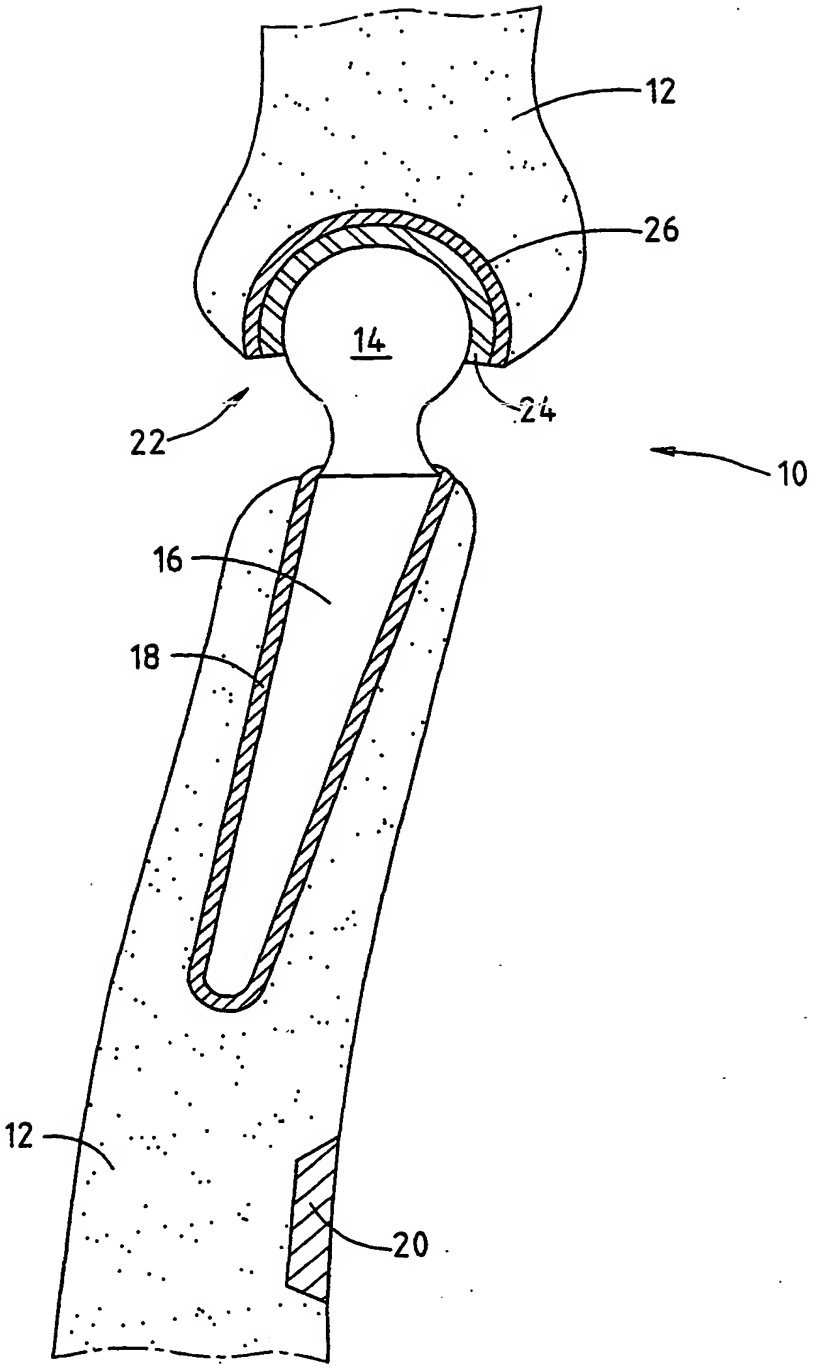

FIG. 1.

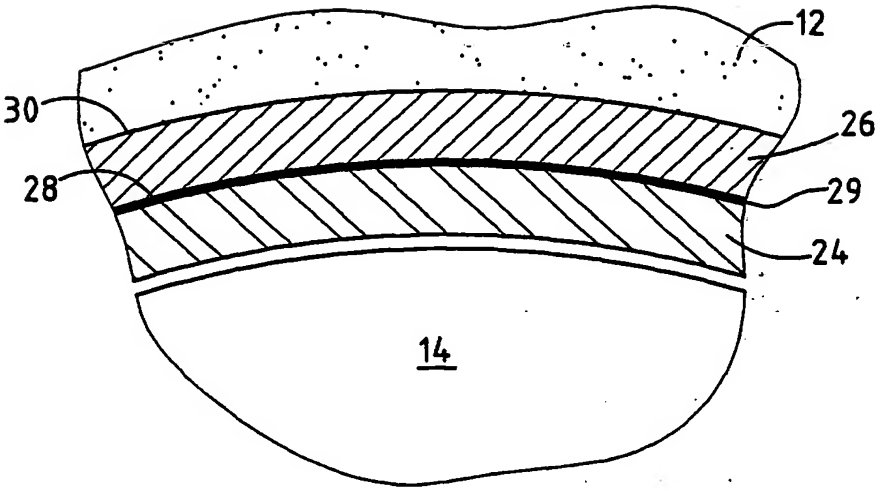

FIG. 2.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/NL 01/00589

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F2/30 A61F2/28 A61L27/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	page 7, line 6 - line 8 abstract; figures	1,11,17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2001	04/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Klein, C

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INTERNATIONAL SEARCH REPORT

International Application No
P../NL 01/00589

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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